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(54) Title: DELAYED AND SUSTAINED RELEASE FORMULATIONS AND METHOD OF USE THEREOF

(57) Abstract: Modified release formulations for the delivery of pain management drugs and/or NSAIDs are provided, which exhibit an initial predetermined delay in drug delivery followed by sustained release of the drug from the formulation.

DELAYED AND SUSTAINED RELEASE FORMULATIONS AND METHOD OF USE THEREOF

FIELD OF THE INVENTION

This invention relates to oral formulations of drugs that are known to cause gastro-intestinal distress, such as pain medications and non-steroidal anti-inflammatory drugs (NSAID), which have excellent delayed release properties, thus eliminating gastro-intestinal side effects. In particular, this invention relates to formulations providing reduced variability in plasma concentrations of pain management drugs and/or NSAIDs, reduced variability in time required to attain maximum plasma concentrations of pain management drugs and/or NSAIDs, and reduced gastrointestinal side effects.

BACKGROUND OF THE INVENTION

A critical need exists for a dosage form that makes drugs used in pain management, such as codeine, morphine, and the like, and non-steroidal anti-inflammatory drugs (NSAID), such as diclofenac, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone, piroxicam, sulindac, salicylic acid, acetylsalicylic acid and the like to begin releasing the drug and reach maximum concentration in blood in both fed and unfed conditions at predictable times, and as a result provide predictable therapeutic effect. It is also necessary that drugs such as those listed above begin to release in the body at predictable times, in order to avoid or reduce undesirable gastrointestinal side

effects. Since peptic ulceration and gastrointestinal bleeding have been reported in patients receiving NSAIDs and many drugs used for management of pain, e.g., acetylsalicylic acid, it is recommended that patients be maintained on the lowest dose possible, consistent with achieving a satisfactory therapeutic response and that the drug be administered with food, and not in a fasting state. Yet, the medical art previously lacked a dosage form for administering a NSAID or pain management drugs that provides therapy with a predictable delay followed by predictable time to reach maximum level of drug in the blood for this application especially when given with food.

As is well known, the maximum time effectiveness in many pharmaceutical preparations containing a drug is only a few hours because of biological modification and elimination of the medication in the body. Consequently, repeated doses must be taken at frequent intervals to obtain long term therapeutic levels of drugs. After high initial peak concentrations, the level of drug in the blood stream continually decreases due to biological elimination, so there is little or no therapeutic effect at the end of the period between doses. As a result, the therapeutic effect fluctuates between doses corresponding to the peaks and valleys in the level of drug in blood.

Many attempts have been made to develop either delayed and/or sustained-release pharmaceutical NSAID preparations or pain management drug formulations. For example, Diclofenac, 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium or monopotassium salt, is a nonsteroidal anti-inflammatory drug (NSAID) that is utilized in the treatment of the acute and chronic signs and symptoms of osteoarthritis and rheumatoid arthritis. Diclofenac is sold commercially as immediate release, delayed release (enteric coated) and extended-release (sustained-release) dosage forms. A commercially available delayed-release diclofenac formulation, Voltaren, available from Novartis Pharmaceuticals, demonstrates that peak plasma levels are achieved in two hours in fasting conditions with a range of about 1 to 4 hours after administration. When Voltaren is taken with food, there is usually a delay in the onset of absorption of 1 to

4.5 hours and most significantly, there is a 40% reduction in peak plasma level when compared to administration under fasting conditions. A commercially available extended release formulation of diclofenac, Voltaren-XR, demonstrates similar amounts of absorption of diclofenac under fed and fasting conditions, however, food significantly alters the absorption pattern of diclofenac. Under fasting conditions, the plasma levels in patients receiving the Voltaren-XR formulation are characterized by multiple peaks and high intersubject variability in blood profiles, while under fed conditions, the plasma levels for patients given Voltaren-XR exhibit a single peak, which usually occurs at about 5 to 6 hours, but the timing often varies significantly. This can cause variations in the therapeutic effect. Additionally the peak plasma concentrations when given under fasting conditions are as high as those when given under fed conditions. This may increase the risk of GI side effects under fasting condition.

The activity of diclofenac and other NSAIDs in humans is directly related to its blood or plasma concentration. For illnesses which require continuous and constant control, such as chronic osteoarthritis and rheumatoid arthritis, NSAIDs generally require administration 3 times a day. After each administration of NSAIDs a succession of rapidly increasing and decreasing plasmatic diclofenac concentrations is established. Thus, the patient being treated and the target organ, as well as the gastrointestinal tract, are alternatively subjected to overdoses and underdoses of medicine.

The side-effects caused by the rapid increase of a NSAID in the blood, e.g. a wide variety of gastrointestinal complaints, can be problematical. As the therapeutic treatment of a rheumatic inflammation always constitutes a compromise between a successful control of the symptoms, which requires an adequate blood plasma level of an anti-inflammatory agent such as diclofenac or other NSAID, and an acceptance of undesirable side-effects, which, as is known, is decisively influenced by excessively high blood plasma values, attempts have already been made to control these side-effects by influencing the release of NSAIDs.

U.S. Patent No. 4,944,949 to Story and Flynn discloses pharmaceutical compositions for use in the treatment of inflammatory arthropathy which include micelles of NSAIDs, such as diclofenac. This formulation provides protection to the stomach and intestine while enhancing the absorption of the NSAIDs. However this formulation does not provide for sustained release of the drugs.

U.S. Patent No. 4,980,170 to Schneider *et al.* describes a controlled release diclofenac formulation where the formulation contains (a) pellet which provides a retarded release diclofenac component, (b) pellets which provide a diclofenac component resistant to gastric juices by encasing with a pH dependent polymer. This formulation containing pellets (a) and (b) thereby provides a pH dependent release and sustained release delivery of diclofenac, but requires mixing of different types of pellets to achieve this effect.

U.S. Patent No. 4,948,581 to Sawayanagi and Otani discloses a long acting diclofenac formulation where the formulation has a rapidly dissolving component providing quick pharmaceutical action and an enteric component providing a delayed pharmaceutical action. The diclofenac formulation was provided by mixing the rapidly dissolving component with the enteric component and filling capsules with the resulting mixture. This means no sustained action and again release from the enteric coated pellets is pH dependent, which is not desirable.

U.S. Patent No. 5,874,107 to Fischer and Klokkers discloses a controllable release formulation of diclofenac formulation. This formulation provides a tablet having two portions of varying ratios of diclofenac and methylhydroxypropylcellulose; (a) one portion with a ratio of >0.3 and a (b) a second portion with a ratio of < 0.3, where the 2 portions (a) and (b) are pressed together to form a tablet. This formulation has an initial delay period of less than an hour followed by a release period.

There is a need for an improved and safer form of administration of drugs for pain management and/or NSAIDs to give protection to the stomach and to reduce the intersubject variability in time required to attain maximum plasma levels of the drug and to reduce the intersubject variability of plasma levels of the drug. Moreover,

there is a need for a formulation that eliminates or reduces the gastrointestinal side effects that often occur when an NSAID or pain management drug by delaying the release predictably rather than relying on a pH dependent type of delay, such as an enteric coating. It is also desirable to reduce the rate of absorption and hence the peak plasma levels should a patient take the formulation in fasting condition.

It is immediately apparent in the light of the above that a pressing need exists for a dosage form that can delay the delivery of a pain management or anti-inflammatory therapeutic, such as diclofenac to provide a drug-free interval independent of pH and then deliver an effective dose of therapeutic agent at a controlled maximum drug concentration in the plasma to thereby avoid rapid or sudden increase of the drug in the blood while still providing a sustained controlled release. It is also desirable that peak plasma levels occur at predictable times with little variation. It will be appreciated by those versed in the medical art, that if a novel and unique dosage form for a therapeutic agent such as diclofenac is made available for executing a therapeutic program comprising a drug-free interval that is not dependent upon pH environment followed by a drug delivery interval wherein the peak concentration of the drug is reached more predictably thereby providing predictable therapeutic outcome and a sustained controlled delivery would represent a valuable contribution to the medical arts. It is also desirable that a pain management drug formulation or NSAID formulation exhibit decreased variability of peak concentration when taken with food and decreased peak concentration when taken during a fasting state. The present invention provides such formulations.

SUMMARY OF THE INVENTION

The present invention provides dosage forms for the oral delivery of a pain management drugs and non-steroidal anti-inflammatory drugs (NSAID) comprising biologically inert pellets coated with an inner layer of drug, i.e., pain management drug or NSAID or a pharmaceutically acceptable salt thereof admixed with a binder agent; and an outer rate controlling layer comprising a water insoluble polymer. In a preferred embodiments the binder agent is present in an amount of from about 10%

to about 35% of the total weight of the drug or NSAID and the outer rate controlling layer polymer is present in an amount of from about 4% to about 10% of the total dry weight of the formulation.

In another aspect of the invention there is provided a method for treating osteoarthritis or rheumatoid arthritis comprising orally administering a diclofenac dosage form comprising a biologically inert pellet having coated thereon a layer comprising about 50 to about 250 mg diclofenac or a pharmaceutically acceptable salt thereof and a binder agent, said binder agent present in an amount of about 10% to about 35% of the total weight of the NSAID, and an outer rate controlling layer comprising a water insoluble polymer present in an amount of from about 4% to about 10% of the total dry weight of the formulation.

In yet another aspect of the invention there is provided a method for the production of a dosage form of a pain management drug or a NSAID which comprises:

1) coating a biologically inert pellet with a dose of a pain management drug or a pharmaceutically acceptable salt thereof, said pain management drug or NSAID being admixed with a binder agent present in an amount of about 10% to about 35% of the total weight of the pain management drug or NSAID to form a drug or NSAID loaded pellet, and

2) coating the drug or NSAID loaded pellet with an outer rate controlling layer of a pharmaceutically acceptable water insoluble polymer, said water insoluble polymer being present in an amount of from about 4% to about 10% of the total dry weight of the formulation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of the core of the structure of a modified release delivery formulation of the invention.

Figure 2 is a graph of the *in vitro* release of a diclofenac modified release delivery formulation of the invention and the currently marketed Voltaren-XR diclofenac formulation over a 24 hour period.

Figure 3 is a graph of the *in vivo* peak plasma concentration under fasting conditions of a diclofenac modified release delivery formulation and the currently marketed Voltaren-XR diclofenac formulation over a 24 hour period.

Figure 4 is a graph of the time required for plasma levels to reach a maximum concentration in individuals under fed conditions for a diclofenac modified release delivery formulation and the currently marketed Voltaren-XR diclofenac formulation.

DETAILED DESCRIPTION OF THE INVENTION

This invention, as disclosed and described herein, provides novel modified release formulations of drugs used for management of pain and/or inflammation, which cause gastro-intestinal distress when administered orally. As used herein the phrase "pain management drug" includes any narcotic or non-narcotic pain reliever (analgesic), which is used in the management of mild to severe pain and/or fever. Such pain management drugs include, for example, codeine, morphine, hydromorphine, anilevidine, merperidine, methadone, levorphanol, pentazocine, propoxyphene, and the like, as well as combinations thereof. The anti-inflammatory drugs include NSAIDs, such as diclofenac, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, phenylbutazone, sulindac, piroxicam, salicylic acid, acetylsalicylic acid and the like that provide sustained release of the NSAID following an initial pH independent delayed release. It is also understood that some of the NSAIDs may also be pain management drugs and/or antipyretic agents, such as for example, acetylsalicylic acid, ketoprofen and the like. The formulations of the invention may also contain a combination of a pain management drug and NSAID. This invention provides pain management drug formulations and/or NSAID formulations that optimize pain management drug and/or NSAID plasma levels by providing a formulation which exhibits a predictable time to reach

maximum blood concentration levels of active agent and provides less variation in maximum blood concentrations than prior art formulations.

The present invention provides novel formulations of pain management drugs and/or NSAIDs characterized by a release profile that results in enhanced pharmacokinetic performance and reduced intersubject variability in rate of absorption and plasma concentrations of active ingredient. This formulation also affords excellent bioavailability while avoiding high plasma concentration peaks in fasting condition to minimize gastro-intestinal tract side-effects while maintaining the extent of absorption, i.e., bioavailability.

The delayed release pain management drug and/or NSAID formulations of the invention exhibit a time dependent release of drug, rather than a pH-dependent release exhibited by prior art formulations that depend on an outer pH-sensitive enteric coating to delay release. Release of drug from the formulations of the present invention does not occur until the formulation has emptied out of the stomach. As a result, the formulations of this invention are not effected by pH variations among individuals and thus, minimize any gastro-intestinal side effects that normally occur with the use of such drugs. Because the release of drug from the formulations of this invention is not pH dependent, the release of drug is more predictable and consistent.

According to the present invention and as illustrated in Figure 1, the modified release formulation is characterized by having a single biologically inert pellet (core) coated by one or more layers of pain management drug and/or NSAID and an outer rate controlling coating. In one embodiment of the invention, the one or more layers of pain management drug(s) and/or NSAID may be seal coated. In accordance with the present invention, any NSAID or its pharmaceutically acceptable salt, and preferably diclofenac or any pharmaceutically acceptable salt of diclofenac may be used as the drug. For example, such salts may include the sodium or potassium salts. It is preferred however, that the sodium salt of diclofenac be used. Any pain management drug that causes gastro-intestinal distress when delivered orally may be used in the present formulations.

The formulations of this invention also permit the use of a NSAID in combination with a second drug, different from the NSAID but useful in combination therewith, which drug may be placed in the drug layer. In a preferred embodiment, the NSAID is used in combination with a pain management drug.

Many types of pellets that are suitable for use in forming the core of the formulations of the present invention are commercially available from a number of pharmaceutical supply companies; for example, non-pareils, sugar and/or starch-based pellets. Non-pareil pellets of particle size 25 to 30 mesh are particularly preferred, although any non-pareil pellet of mesh size within the range of 14 mesh to 60 mesh are also preferred for use in this invention. Alternately granules can be prepared by conventional techniques known in the art containing the drug.

Suitable binder agents for use in the drug layer of the formulations of the present invention include, for example, hydroxypropylmethyl cellulose (3 to 6 cps, preferably 6 cps), hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidone and the like. Preferably, hydroxypropylmethyl cellulose is used in the practice of the present invention. Preferably, the binder agent is dissolved in water (or any suitable solvent) to form a 5% to 30% (w/w) solution, preferably a 7% to 25% (w/w) solution and most preferably, an approximately 10% (w/w) solution. The solution of binder agent is admixed with a solution or suspension of the pain management drug and/or NSAID and any other therapeutic agent to be combined with the drug(s), and then applied onto the pellets by conventional film (or spray) techniques.

For example the drug/binding agent solution may be applied to the pellets by spraying the solution or suspension onto the pellets using a fluid processor. The binder agent constitutes about 10-35%, preferably about 15-30%, and most preferably about 20-27% of the total weight of drug in the formulation.

The drug layer of the modified release formulations of the present invention may include one or more pharmaceutically acceptable excipients in addition to the pharmacalogically active agent(s) and binder agent. Pharmaceutically acceptable excipients which may be employed are well known to those of skill in the art and

include any conventional pharmaceutically acceptable excipient, such as an antifoam agent, which is added to aid the formulation process. The drug layer may include a suitable carrier or diluent, and may optionally contain a surfactant. In another embodiment of the invention, the drug layer may be coated with a sealing layer.

The optional sealing layer contains a water soluble polymer, which may be the same or different from the binder agent present in the drug layer. For example, the sealing agent may include a water soluble polymer such as hydroxypropylmethyl cellulose (3 to 6 cps, preferably 6 cps), hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinylpyrrolidone and the like. Preferably, hydroxypropylmethyl cellulose, and most preferably, hydroxypropyl-methyl cellulose-E-6 is used in the sealing layer.

The total amount of optional sealing layer contained in the pharmaceutical loaded pellets may be varied. The sealing layer may constitute from about 0.5 to 5% of the total weight of the formulation.

The drug and/or NSAID loaded pellets are substantially enveloped with a layer of a water insoluble polymer referred to herein as a"rate controlling layer." The rate controlling layer sufficiently protects the integrity of the drug-loaded pellets for the desired period of time. As a consequence, the release or delivery of the pain management drug and/or NSAID is inhibited for a predetermined amount of time after oral administration. Once the desired, pre-delivery time has elapsed the drug is released at a rate that provides decreased variation in plasma concentrations of pain management drug and/or NSAID and decreased intersubject variability in attaining maximum blood plasma concentration as compared to prior art drug or NSAID formulations.

The rate controlling layer may be comprised of ethyl cellulose, a copolymer of acrylic and methylacrylic acid esters, which is physiologically acceptable, water insoluble, and permeable to the release of the pain management drug and/or NSAID or a pharmaceutically acceptable salt thereof, such as Eudragit RL 30 D, Eudragit RS 30D, or a poly(meth)acrylate polymer, such as Eudragit NE 30 D or Eudragit NE40D, or a combination thereof. Most preferably, the poly(meth)acrylate

polymer, Eudragit NE 30 D, is used in formulating the controlled release coating. Eudragit NE 30 D, Eudragit NE40D, Eudragit RS 30 D and Eudragit RL 30 D polymers are available from Rhom Pharma, D-6108 Weiterstadt 1, Dr. Otto-Rohm-Str. 2-4, Germany. Eudragit NE 30 D and Eudragit 40D are pH independent polymers available as 30% or 40% aqueous dispersions, respectively. Eudragit RS and Eudragit RL 30 D are available as aqueous dispersions containing 30% dry substances. The NE30D solids in the rate controlling layer generally constitutes about 4%-30% of the total weight of the solids content of the present formulations, preferably about 5%-20%, and most preferably about 6%-10% of the total weight of the solids content of the present formulations. In a preferred embodiment of the invention the binder agent used in the drug layer is hydroxypropylmethyl cellulose and the outer rate controlling layer is Eudragit NE 30 D.

In a preferred embodiment, the rate controlling layer contains in addition to a water insoluble polymer an amount of a lubricant, such as for example, calcium stearate, magnesium stearate, zinc stearate, stearic acid, talc or a combination thereof to form the rate controlling layer. In particular, it is preferred that the outer rate controlling layer contains an amount of magnesium stearate sufficient or other lubricant to provide delayed release of diclofenc for up to about 4-5 hours after administration of the formulation. In a most preferred embodiment the outer rate controlling layer contains a combination of magnesium stearate and talc admixed with the water insoluble polmer, which is preferably Eudragit NE30D. The lubricant functions to prevent agglomeration of the coated pellets during processing and also helps to delay release of the pharmaceutical agent from the coated pellets. The optional presence of talc in the outer rate controlling layer also helps to delay release of the pharmaceutical agent from the coated pellets and prevent agglomeration during processing.

In a preferred embodiment, the final, dried controlled release coating contains about 0.5-5.0% magnesium stearate and/or other lubricant agent(s), and more preferably about 0.5%-3.0%, and most preferably about 0.5%-0.8 % lubricant

agent based on the total weight of solids content of the total formulation. The outer rate controlling layer also preferably contains from about 0.5%-5% talc, preferably about 1%-3% talc, and most preferably about 1.5%-2.5% talc based on the total weight of the formulation. The presence of an amount of about 0.5%-1.0% w/w magnesium stearate or other lubricant and about 1%-3% of total formulation of talc in the controlled release coating helps to delay release of the drug following oral administration of the formulation.

Optionally, the rate controlling layer may contain an amount of a water soluble polymer in addition to the water insoluble polymer.

In another embodiment of the invention the outer rate controlling layer is coated with an enteric coating polymer, which may optionally contain a plasticizer. A preferred enteric coating polymer is Euragit L 30D. Suitable plasticizers for inclusion in the enteric layer include, for example, triethyl citrate, polyethylene glycol, dibutyl phthalate, diethylphthalate and triacetin. The optional enteric coating, which is pH dependant and resistant to gastric fluids may comprise from about 3-10%, preferably about 4-6% of the total weight of solids content of the formulation. The enteric coating and/or the rate controlling layer may also be coated with one or more layers of a sealant or a binding agent.

The pain management drug and/or NSAID layer, optional sealing layer, outer rate controlling layer and optional enteric coating may each further comprise diluents, carriers, fillers and other pharmaceutical additives which may or may not effect the rate of release of active agent(s) from the single pellet. For example, the outer rate controlling layer preferably contains a lubricant agent(s) and the drug layer may optionally contain surfactants. The pellet layers may further contain pharmaceutically acceptable excipients such as anti-adherents, pharmaceutically acceptable pigment such as, titanium dioxide, iron oxide and various color pigments including vegetable dyes, and the like.

Preferably, the pharmaceutical loaded pellets of the invention provide in total a potency of approximately 50% (w/w) based upon the total weight of the layered pellets, although the potency can be adjusted as desired. For example, when the

pharmaceutical agent included in the layering is diclofenac, it is preferred that the layered pellet be formulated at about 45 to about 55% potency (w/w). However, the skilled practitioner can formulate the modified release formulations of the invention to have any desired total potency of pain management drug and/or NSAID.

Depending upon the specific pain management drug or NSAID present in the modified release formulations the dose of drug(s) will vary. For example, diclofenac is generally recommended for use in the treatment of rheumatoid arthritis and other rheumatoid disorders at a dose of from 50 to 150 mg per dose, depending on the form of administration and frequency (usually three time per day). Flufenamic acid is usually prescribed for rheumatic disorders at doses of from 400 to 600 mg per day in divided doses; flurbiprofen is recommended for use at doses of from 150 to 200 mg per day (up to 300 mg per day); ibuprofen is recommended for use at from 200 to 1200 mg per dose (up to 2,400 mg per day); indomethacin is recommended at a dosage of 150 to 200 mg per day in divided doses; ketoprofen is recommended at a dosage of from 50 to 100 mg twice daily; naproxen is recommended at a dosage of from 500 to 1,000 mg daily in divided doses; phenylbutazone is recommended at a dosage of from 200 to 300 mg per day in divided doses; piroxicam is recommended at a dosage of from 10 to 30 mg per day; and sulindac is recommended at a dosage of from 400 to 600 mg per day. Codein is routinely recommended at a dosage of 10 mg to 60 mg depending on the severity of pain, to be taken every 4 to 6 hours as needed. The dosage amount of any of the pain management drugs and NSAIDs used in the invention can readily be determined by those skilled in the art. Of course, those skilled in the art will recognize that the dosage amount can be varied according to a patient's needs, e.g., adult versus child, other medications being administered, etc.

The modified release formulation, as disclosed herein, permits the delayed release of the pain management drug and/or NSAID, or a pharmaceutically acceptable salt thereof, in a manner to provide and maintain a reduced variability of plasma drug concentrations and timing of maximum plasma concentrations in comparison to that attained with prior art diclofenac formulations. The formulations

of the present invention preferably provide an approximately 4-5 hour initial pH independent delay in drug release, although the initial delay in release of drug may be varied by increasing or decreasing the thickness of the outer rate controlling layer and/or manipulating the levels of water insoluble polymer, lubricant(s) and talc components of the rate controlling layer. Following the initial delay in drug release, the drug is released in a sustained manner to provide drug plasma levels for up to about 24 hours. The sustained release of drug from the formulations of the invention enables a reduction in the frequency of administration.

The pain management drug and/or NSAID formulations herein, when administered to a patient, e.g., a mammal, particularly a human patient, in a fasting state result in maximum blood plasma concentrations that are lower than observed with prior art formulations, which is a desired characteristic for pain management drugs and NSAIDs because of their propensity to cause gastrointestinal distress when administered in the fasting state. However the extent of absorption is the same. When administered in the fed state (after eating or at the time of eating) the formulations of the present invention are absorbed at a rate and to the extent observed with prior art formulations. Whether administered in a fasting state or fed state, the percent variation of plasma concentration and percent variation in time required to reach maximum plasma concentrations are lower with formulations of the present invention in comparison to prior art formulations , e.g., Volatren XR, a commercially available diclofenac formulation. Thus the present modified release drug formulations reduce the known problem of high intersubject variability observed with pain management drug formulations and NSAID formulations.

The process for making the pharmaceutical formulations of the present invention includes coating at least one layer of the desired pain management drug and/or NSAID and optionally any other pharmaceutical agent together with a suitable binding agent onto the surface of biologically inert pellets; *i.e.*, layered or a non-pareil pellet (sugar and/or starch-based pellets). The drug layer may optionally be substantially enveloped by a sealing coat layer. The drug layer or optional sealing

coat layer is then substantially enveloped by an outer rate controlling layer of water insoluble polymer, which is optionally coated with an enteric coating.

In preparing the formulations of the invention, the pain management drug and/or NSAID layer may be sprayed onto non-pareil or other pellets or granules that have been suspended in a fluidized bed, for example. Preferably, the binder agent, such as hydroxypropylmethyl cellulose is dissolved in water to form a 5% to 30% (w/w) solution, preferably a 7% to 25% (w/w) solution and most preferably, an approximately 10% (w/w) solution, which is admixed with a solution of the drug(s) and any other desired pharmaceutical agent(s). The solution or suspension of drug(s) and binder agent is then applied onto the pellet using, for example, a fluid processor. Although some organic solvent may be used in the film coating application, the inclusion of organic solvents in the coating solutions used in the present methods is not required.

After the pellets are layered with pain management drug and/or NSAID (and any other desired drug or therapeutic agent) and binder agent to form drug loaded pellets, they may optionally be dried by air exposure, or other methods known in the art (although drying may occur spontaneously from air flow in the fluid bed processor). Pellets obtained from the drug layering are then fluidized and sprayed with the water insoluble polymer coating to form the rate controlling layer.

The polymer comprising the outer rate controlling layer is generally prepared as a dispersion, optionally mixed with lubricant and/or talc and applied onto the prepared pellets. The total amount of rate controlling polymer in the pellets is in the range of from about 3%-10% of the total weight of the prepared pellets, preferably about 5%-8% of the total weight of the prepared pellets, and most preferably about 6%-7% of the total weight of the prepared pellets. By varying the amount of rate controlling polymer within this range, a desired predetermined delay in release of the therapeutic agent is achieved.

At the final stage the pellets may be subjected to a curing process, preferably after application of about 1%-2% dry talc to the coated pellets. The pellets are cured at a temperature in the range of from about 30° to about 50°C, preferably, from

about 35° to about 45°C, and most preferably, about 40°C for a period of about 5 to about 10 days and, preferably, about 7 days. Surprisingly, although others in the art have found shorter curing times to be preferred, the inventor of this invention has found that these long curing times help to stabilize the formulation and aid in delaying the release of pharmaceutical agent from the pellets even after long storage periods and in sustaining release of the formulation.

The cured coated pellets may be weighed out according to the total dose of pharmaceutical agent(s) to be administered to patients. Diluent may be added, such as, for example, dextrose, sorbitol, mannitol, microcrystalline cellulose, methocel ether, lactose, glyceryl palmitostearate, glyceryl stearate, glyceryl behenate, and combinations thereof, among other commonly used pharmaceutical diluents, and the mixture of coated pellets and diluents pressed into tablets. Alternatively, the mixture of the coated pellets alone can be encapsulated in a capsule, such as a hard gelatin capsule.

It is often desirable to add inert diluent when formulating the coated pellets into tablet form. The presence of pharmaceutical diluents, such as microcrystalline cellulose, methocel ether, glyceryl palmitostearate, glyceryl stearate, and/or glyceryl behemate, for example, in the pellet mixture serves to cushion the pellets so that they are not significantly ruptured during compression.

In general, the release rate of pain management drug and/or NSAID from the pellets is dependent upon a number of factors including, *inter alia,* the overall structure and design of the layered pellet, the potency of the layered pellet, the type and amount of polymer admixed with the drug layer and type and amount of polymer and optional lubricant(s)/talc in the outer rate controlling layer. The pellets may be formulated into tablets or encapsulated in the desired dosage amount. Typical unit dosage amounts for the modified release pain management drug and/or NSAID formulations of the invention for oral administration include any dosage between about 15 and 1000 mg, such as 15, 25, 30, 40, 50, 100, 200, 300, 500, 750 mg, depending on the specific pain management drug and/or NSAID of the formulation. The pain management drug and/or NSAID formulations of the invention are

formulated to provide a pharmaceutically effective plasma concentration of drug(s) at a predetermined time after administration,. Because the modified release drug formulations of the present invention is in a multiparticulate, e.g., granular or pellet form, the formulation travels more uniformly through the gastrointestinal tract thereby reducing intersubject variability in maximum pain management drug and/or NSAID plasma concentrations, as shown in Example 2. The release profile of pain management drug and/or NSAID from the formulations of the present invention minimizes gastrointestinal side effects irrespective of whether the patient is in a fed or fasting state.

The following examples are illustrative of the invention, and are not to be construed as limiting the invention.

EXAMPLES

Example 1

Step I. Inner Drug Layering

Diclofenac Formulation

Non-Pareils 25/30 mesh	443 g
Diclofenac sodium hydrochloride (HCl)	636 g
Hydroxypropylmethyl cellulose (HPMC) as 10% w/w solution in water	1590 g
Deionized (DI) water	1879 g
Anti foam as a 30% dispersion	32 g

Method

1. Prepared 10% HPMC solution by dispersing 159 g of HPMC E-6 (6 cps grade of Dow Chemicals) into 1431 g of deionized water and mixed until a clear solution was obtained.
2. Added 1879 g deionized water to the 10% HPMC solution and mixed.
3. Added 16 g antifoam and 636 g diclofenac sodium to the solution and homogenized.
4. Added remaining (16 g) antifoam and mixed for 15 minutes.
5. Sprayed the solution onto non-pareil pellets using a fluid bed processor.

Step II. Outer Layering

Formulation of Outer Rate Controlling Layer

Layered pellets of Step I	750 g
Eudragit NE30D 30% dispersion	500 g
Magnesium Stearate 15% w/w dispersion	100 g
Talc	45 g
DI water	430 g

Method

1. Prepared a 15% magnesium stearate dispersion by adding 15 g of magnesium stearate and
0.5g antifoam suspension to 84.5 g of deionized water and mixing until a homogeneous dispersion was obtained.
2. Added talc to 2/3 of the water and homogenized for 10 minutes.
3. Added the magnesium stearate suspension to the talc mixture and mixed.
4. The Eudragit NE30D dispersion was added to the dispersion of step 3 and mixed for 15 minutes.
5. The remaining water was added and thedispersion was mixed for 10 minutes.
6. 385g of the solution of 5 was sprayed onto the layered pellets using a fluid bed processor.

7. The coated pellets were cured for up to 7 days at 40°C after adding 2% dry talc.

Capsule Filling Step III

Size # 2 capsules were filled with the coated pellets of Step II which were blended with talc (1% w/w). The capsules may be manually filled or machine filled. The fill weight was adjusted to provide the desired strength (i.e. amount of diclofenac per capsule). 218 mg of pellets of Step III were filled at 45.8% potency to give 100 mg of diclofenac per capsule.

Example 2. *In-Vitro* Release of Diclofenac

Dissolution testing was performed on capsules prepared as in Example 1, as well as on a commercially available matrix tablet diclofenac formulation, Voltaren XR. USP Method II, 900 ml de-ionized water, and 100 rpm were used as conditions for testing. Both formulations contain 100 mg diclofenac. Results are shown in Figure 2.

As can be seen from the data in Figure 2, the present formulation provides an initial delay prior to drug release, whereas the comparative diclofenac formulation begins to immediately release drug.

Example 3. *In-Vivo* Release of Diclofenac

A single dose (100 mg), four way randomized crossover pharmacokinetic (PK) study in eight healthy volunteers and scintigraphy study in six healthy volunteers, involving fasted and fed (high fat breakfast) administration was undertaken. The PK study on a modified release diclofenac formulation of the present invention suggested enhanced pharmacokinetic performance and reduced variability compared to the marketed matrix tablet preparation (Voltaren XR). Subsequently, a scintigraphic (SC) study was conducted in order to elucidate the reasons for enhanced performance of the modified release diclofenac formulation of

the present invention compared to the commercially available diclofenac formulation, Voltaren XR.

PK study

In a four way cross-over study, 8 healthy subjects were given either a single dose of the diclofenac formulation prepared as per Example 1 and the marketed diclofenac product, Voltaren-XR under fasting as well as fed conditions and blood was drawn at various times after administration for up to 24 hours. The maximum plasma concentration (Cmax) of diclofenac in the eight individuals for the formulation of the present invention and for Voltaren XR are shown in Figure 3. The time required to reach maximum concentration of diclofenac in the patient s plasma (Tmax) for each formulation is shown in Figure 4.

As can be seen in Figure 3, the present formulation eliminates the variation in Cmax that is typically observed with Voltaren XR. Voltaren XR is absorbed quicker and plasma concentrations of diclofenac are higher than with the formulation of the present invention, which is undesirable with NSAIDs in general because of their propensity to cause gastrointestinal distress.

Figure 4 demonstrates that the formulation of the present invention substantially eliminates variability in the time required to reach maximum plasma concentration of drug, thus removing the guess work involved in administering NSAID therapy.

Diclofenac PK Study Summary

		AUC_{0-t}			C_{max} (ng/mL)			T_{max} (hours)		
		Mean	SD	%CV	Mean	SD	%CV	Mean	SD	%CV
Present Formulation (100 mg diclofenac)	Fasted	2501	567	23	285	62	22	8.6	2.7	32
	Fed	2343	617	26	636	339	53	6.1	0.4	6
Voltaren XR (100 mg diclofenac)	Fasted	2667	860	32	459	227	49	5.8	2.8	49
	Fed	2530	737	29	611	355	58	5.1	3.4	67

AUC: extent of absorption of diclofenac
%CV: percent plasma concentration variability
Cmax: maximum plasma concentration
Tmax: maximum time required to reach maximum plasma concentration

Gamma Scintigraphy Study

A scintigraphic (SC) study was conducted to help elucidate the reasons for enhanced performance of the diclofenac formulation of the present invention in comparison with the commercially available diclofenac formulation, Voltaren XR. The study highlights the effect of formulation differences on the interaction of dosage forms and gastrointestinal physiology, which subsequently influences pharmacokinetic performance.

Both test and reference formulations were labeled by neutron activation(^{153}SM). Six healthy volunteers were given the diclofenac formulation prepared in Example 1 and Voltaren XR in both fasting and fed conditions.

Results. It was observed in the PK study that Cmax under fasting condition for the formulation of this invention was lower (a desired characteristic for NSAIDs) than that for Voltaren XR, yet the extent of absorption (AUC) was comparable for both formulations following fasted administration. These results show that the present NSAID formulation does not compromise bioavailabilty, but reduces the risk of gastrointestinal distress due to low Cmax.

In the fed state, the rate and extent of absorption were similar for both formulations. In either case the percent plasma concentration variability (%CV) for the PK parameters were lower for the diclofenac formulation of the invention compared with Voltaren XR, e.g. 6% concentration variability (CV) for the present diclofenac formulation compared with 67% CV for Voltaren when comparing Tmax under fed state. For the present diclofenac formulation the fed state small bowel transit [5.7± 1.9h] was comparable to that observed following fasted administration [5.1± 2.8h] confirming that the dietary state at the time of dosing has little or no effect on small bowel residence time for the present formulations.

In contrast, in the fasted state, gastric emptying (GE) of Voltaren XR occurred on average at 0.5 ± 0.2 h with a range of 0.2 - 0.9 h. In one volunteer in the fasted state, complete disintegration of the tablet matrix occurred prior to colon arrival; arrival in the large bowel occurred on average at 4.6 h after GE for the other subjects. The anatomical site of complete disintegration in the fasted state for the Voltaren XR product was highly variable, ranging from the small intestine to the descending colon; disintegration times ranged from 5.0 h to in excess of 24 h for this monolithic product. Following fed administration, complete disintegration of the Voltaren tablet formulation occurred in the stomach in many individuals. In those subjects where prolonged stomach residence time was observed complete disintegration occurred relatively quickly and on average disintegration time in the fed state was 7.2 ± 2.0 h. This suggests that there is a significant food effect on the Voltaren formulation *per se* induced by ingestion with a high fat meal.

Conclusions. The study highlights the effect of formulation differences on the interaction of dosage forms and gastrointestinal physiology, which subsequently influences pharmacokinetic performance.

Example 4. Treatment of Osteoarthritis and Rheumatoid Arthritis

Pellets are prepared as described in Example 1, compressed into tablet form or capsule form, and formulated to contain a desired dosage of 100 mg diclofenac. A tablet or capsule are then orally administered to a patient in need of treatment of

osteoarthritis or rheumatoid arthritis. The dosage form can be administered upon need to the patient in either a fasting or fed state for relief of pain. This drug treatment may be continued as needed to control disease symptoms.

It should be understood that some modification, alteration and substitution is anticipated and expected from those skilled in the art without departing from the teachings of the invention. Accordingly, it is appropriate that the following claims be construed broadly and in a manner consistent with the scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. A dosage form for the oral delivery of a pain management drug and/or non-steroidal anti-inflammatory drug (NSAID) comprising:

a biologically inert pellet having coated thereon:

an inner layer comprising a dose of the pain management drug and/or NSAID or a pharmaceutically acceptable salt thereof admixed with a binder agent, and

an outer rate controlling layer comprising a water insoluble polymer.

2. The dosage form of Claim 1 wherein the binder agent is present in an amount of about 10% to about 35% of the total weight of the pain management drug and/or NSAID.

3. The dosage form of Claim 2 wherein the outer rate controlling layer is present in an amount of from about 6% to about 10% of the total dry weight of the formulation.

4. The dosage form of Claim 1 wherein said biologically inert pellet is a non-pareil pellet or granule.

5. The dosage form of Claim 1 wherein said pellet has a particle size of from about 25 to about 30 mesh size.

6. The dosage form of Claim 1 wherein said rate controlling layer additionally contains a lubricant.

7. The dosage form of Claim 6, wherein said lubricant is magnesium stearate, calcium stearate, or zinc stearate.

8. The dosage form of Claim 6 wherein the outer rate controlling layer comprises from about 0.5 to about 5% magnesium stearate of total pellet.

9. The dosage form of Claim 8 wherein the outer rate controlling layer further comprises from about 0.5% to about 5% talc of total pellet.

10. The dosage form of Claim 1 wherein said outer rate controlling layer comprises poly(meth)acrylate polymer or a copolymer of acrylic and methacrylic acid esters, which are physiologically acceptable, water insoluble, and permeable to the release of said NSAID or a pharmaceutically acceptable salt thereof.

11. The dosage form of Claim 10 wherein the outer rate controlling layer comprises Eudragit NE 30D.

12. The dosage form of Claim 11 wherein the outer rate controlling layer further comprises from about 1.5% to about 2.5% talc and from about 0.5 to about 1% magnesium stearate.

13. The dosage form of Claim 1 wherein the outer rate controlling layer is coated with an enteric coating.

14. The dosage form of Claim 12 wherein the inner layer comprises a dose of diclofenac.

15. The dosage form of Claim12 wherein the diclofenac is present in a dosage form amount of 100 mg.

16. The dosage form of Claim 1 wherein the pain management drug and/or NSAID provides overall drug potency of about 40% to about 55% w/w.

17. The dosage form of Claim 1 in a tablet or capsule form.

18. The dosage form of Claim 1 wherein said dosage form exhibits a delay in release of pain management drug and/or NSAID of from about 4 to about 5 hours following administration.

19. The dosage form of Claim 18 wherein the NSAID is diclofenac.

20. The dosage form of Claim 1 wherein the inner layer is coated with a sealing layer.

21. A method of treating or controlling osteoarthritis or rheumatoid arthritis, in a subject in need thereof, comprising orally administering to said subject a diclofenac dosage form comprising a biologically inert pellet having coated thereon a layer comprising about 50 to about 250 mg diclofenac or a pharmaceutically acceptable salt thereof and a binder agent, said binder agent present in an amount of about 10% to about 35% of the total weight of the diclofenac, and

an outer rate controlling layer comprising a water insoluble polymer present in an amount of from about 4% to about 10% of the total dry weight of the formulation.

22. The method of Claim 21 wherein the dosage form is administered under fasting conditions.

23. The method of Claim 21 wherein the dosage form is administered under fed conditions.

24. The method of Claim 21 wherein the plasma concentration of diclofenac reaches a maximum concentration at about 5 to 8 hours following administration

25. The method of Claim 21 wherein said dosage form exhibits a delay in release of diclofenac of from about 3 to about 5 hours following administration.

26. The method according to Claim 21 wherein the outer rate controlling layer comprises a water insoluble copolymer of acrylic and methylacrylic acid esters, which is physiologically acceptable, and permeable to the release of diclofenac or a pharmaceutically acceptable salt thereof.

27. The method of Claim 21 wherein the outer rate controlling layer of said dosage form further comprises from about 0.5 to about 5% magnesium stearate.

28. The method of Claim 21 wherein the layer of diclofenac is coated with a sealing layer.

29. A method for the production of a pain management drug and/or NSAID dosage form which comprises:

1) coating a biologically inert pellet or granule with a dose of a pain management drug and/or NSAID or a pharmaceutically acceptable salt thereof, said pain management drug and/or NSAID being admixed with a binder agent present in an amount of about 10% to about 35% of the total weight of the pain management drug and/or NSAID to form a drug loaded pellet, and

2) coating the pain management drug and/or NSAID loaded pellet with an outer rate controlling layer of a pharmaceutically acceptable water insoluble polymer, said water insoluble polymer being present in an amount of from about 6% to about 10% of the total dry weight of the formulation.

30. The method of Claim 29 wherein the dosage form comprises diclofenac.

31. The method of Claim 29 wherein the dose of diclofenac is coated with a sealing layer.

32. The method of claim 31 wherein the outer rate controlling layer is coated with a sealing layer.

DICLOFENAC CR SCHEMATIC

1=RATE CONTROLLING MEMBRANE

2=DRUG LAYER

3=CORE

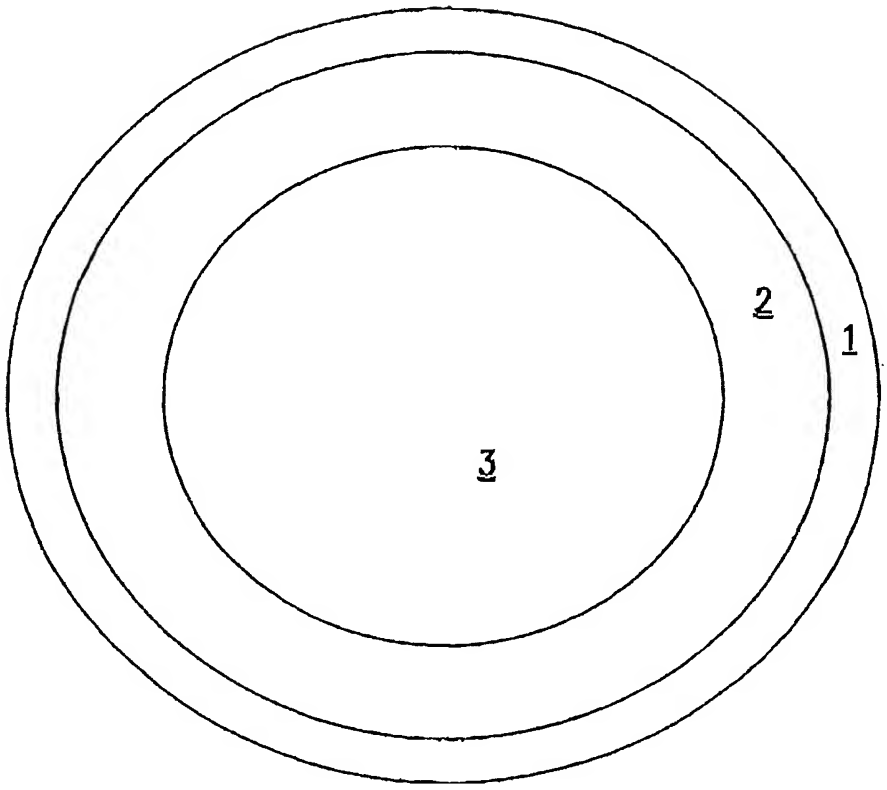
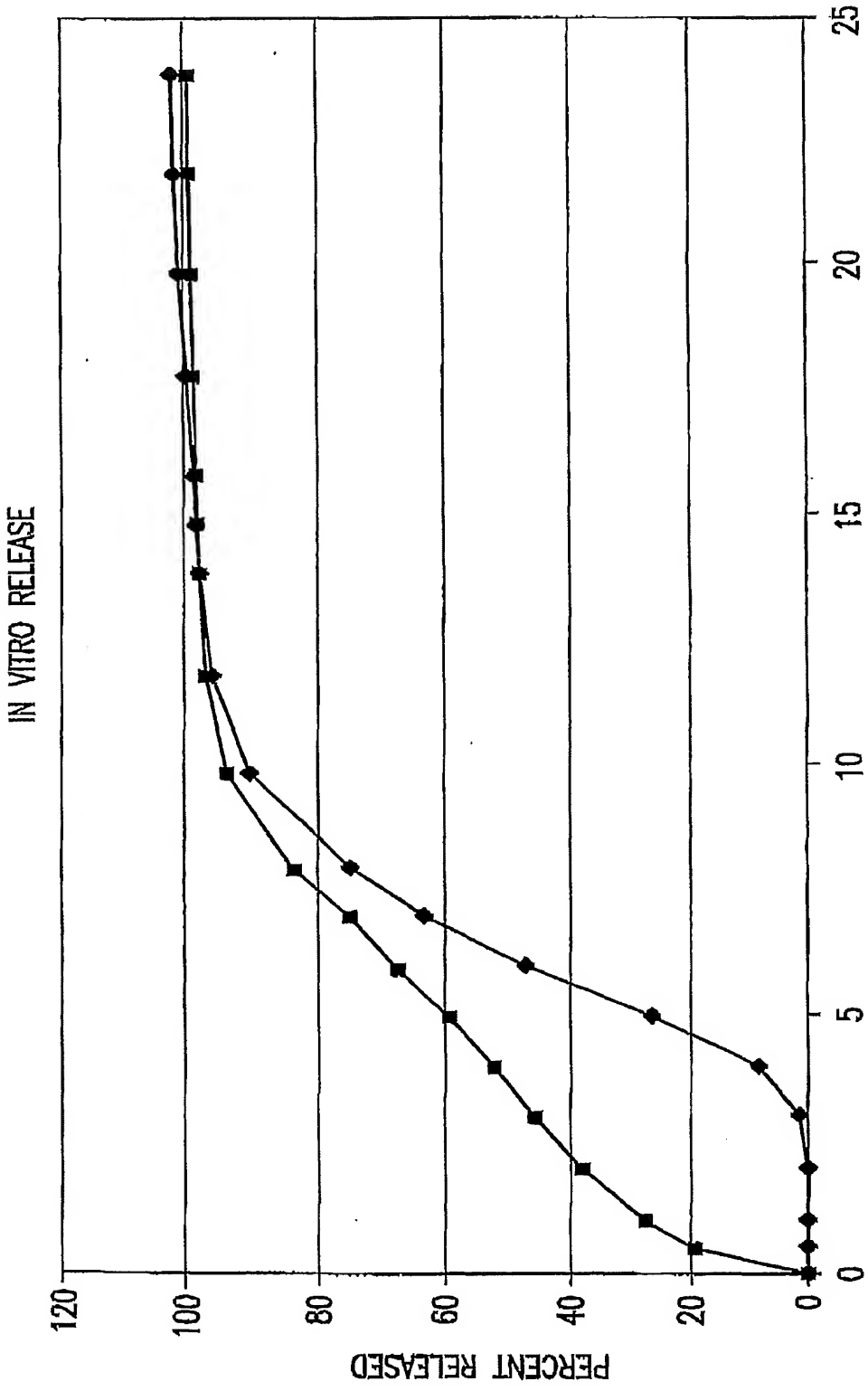


FIG. 1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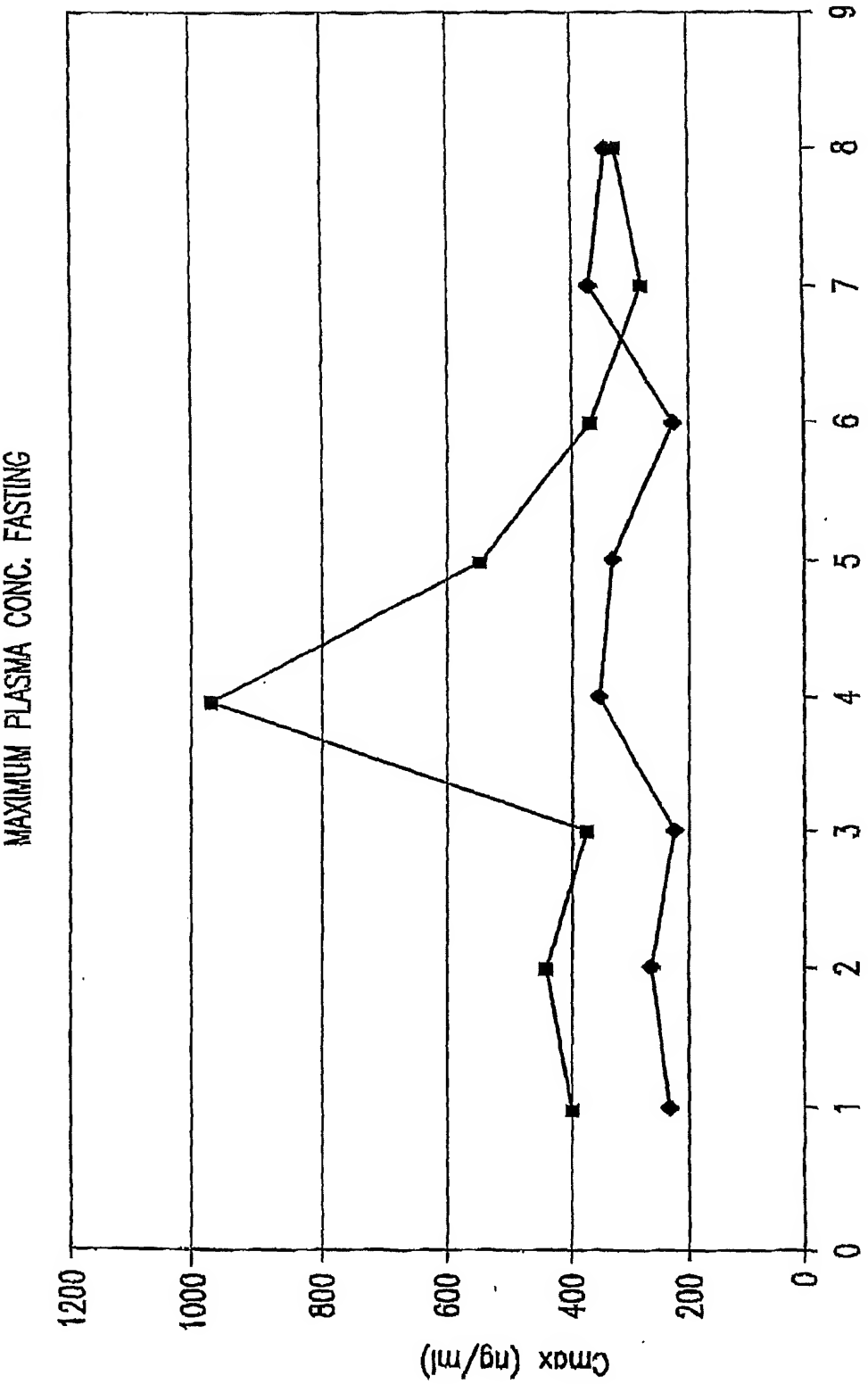
INVENTION
VOLTAREN XR

FIG.2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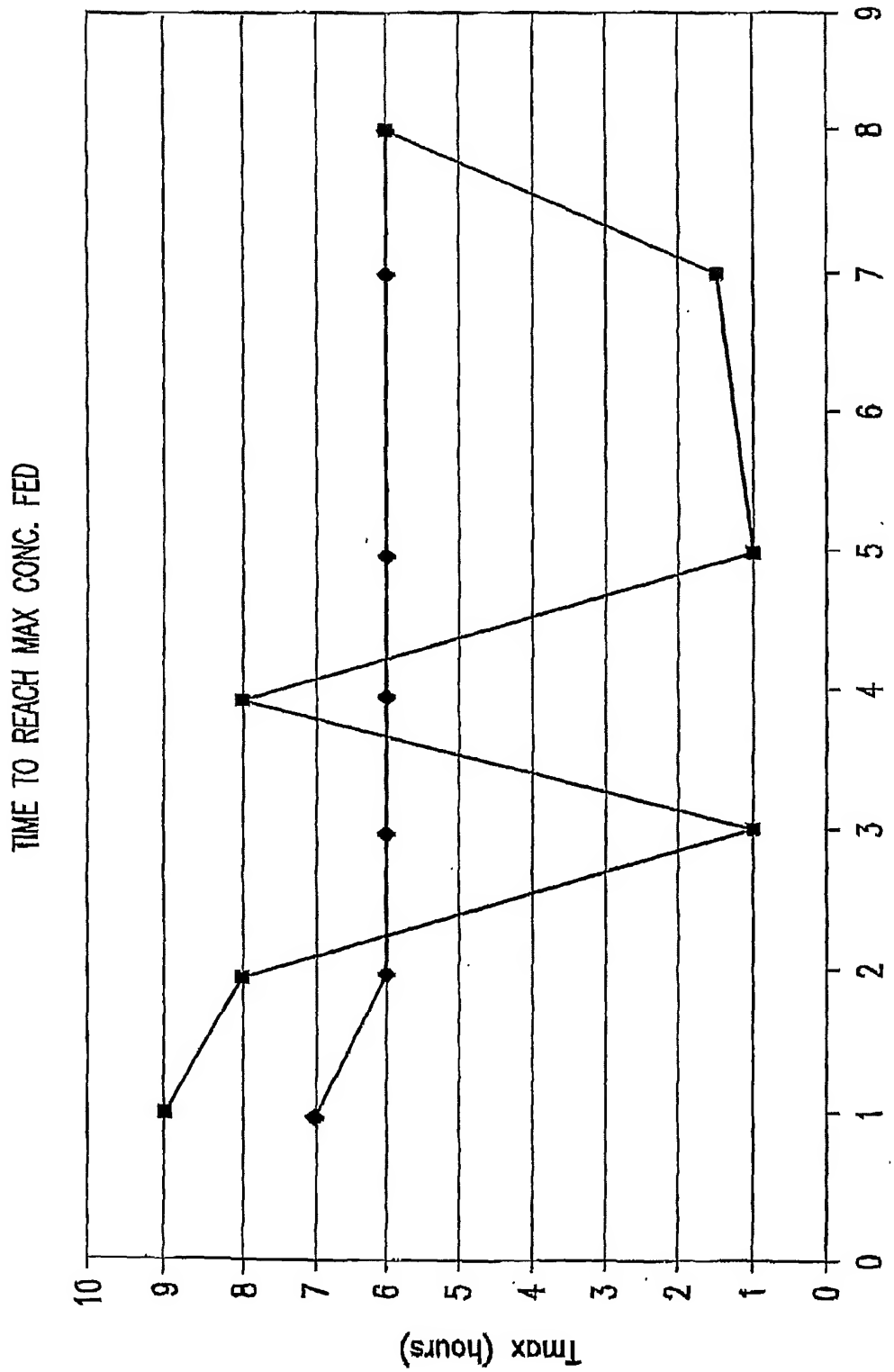
SUBJECTS
INVENTION
VOLTAREN XR

FIG.3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SUBJECTS
INVENTION
VOLTAREN XR

FIG.4

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10 October 2002

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(54) Title: DELAYED AND SUSTAINED RELEASE FORMULATIONS AND METHOD OF USE THEREOF

(57) Abstract: Modified release formulations for the delivery of pain management drugs and/or NSAIDs are provided, which exhibit an initial predetermined delay in drug delivery followed by sustained release of the drug from the formulation.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 01/32446

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/54 A61K31/196 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 711 967 A (JUCH) 27 January 1998 (1998-01-27)	1-6, 9-11,13, 16,17, 21-23, 26,29,30
Y	column 1, line 60 -column 2, line 44 column 3, line 57 -column 6, line 56 column 10 -column 11; example 3	7,8,12, 14,15, 18,19, 24,25,27
Y	EP 0 605 174 A (KINAFORM TECHNOLOGY INC.) 6 July 1994 (1994-07-06) page 6 -page 7; example 3	7,8,12, 14,15, 18,19, 24,25,27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

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'O' document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2002	12/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/US 01/32446

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte nal Application No
PCT/US 01/32446

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